# PHARMACEUTICAL COMPOSITIONS OF MACROLIDES OR CYCLOSPORINE WITH A POLYETHOXYLATED SATURATED HYDROXY-FATTY ACID

[0001] This invention relates to medicinal preparations for peroral administration containing a cyclosporin, especially cyclosporin A, or a macrolide, e.g. a rapamycin or an ascomycin, as pharmaceutically active agent.

[0002] Cyclosporins are cyclic oligopeptides of biological origin, which are used in particular as immunosuppressants. The cyclic polypeptide cyclosporin A consists of 11 amino acids. As a highly effective immunosuppressant, when tested on animals it prolongs the life of allografts, for example of skin, heart or kidneys. Research has shown that cyclosporin inhibits cell-linked reactions, the delayed hypersensitivity of the skin, graft-versus-host disease and T-cell-dependent antibody production. For this reason, cyclosporins are employed in organ transplants to prevent rejection reactions. Since, in contrast to other immunosuppressants, these compounds have only very low bone marrow toxicity, they are also used in the case of bone marrow transplants.

[0003] In addition, it is known that cyclosporins possess anti-inflammatory and anti-parasitic activity.

[0004] The use of the cyclosporins is therefore not restricted to immunosuppressants, but may be extended to the therapy of various auto-immune diseases and inflammatory conditions, especially also to the treatment of inflammatory disorders in which auto-immune processes play a role. These include arthritic illnesses, e.g. rheumatoid arthritis or other rheumatic disorders.

[0005] As anti-parasitic agents, cyclosporins may be used to treat protozoal infections such as malaria.

[0006] However, with the cyclosporin preparations that have been employed in practice for a long time, potentially serious side effects have had to be taken into account, in particular with regard to kidneys. In addition, It is known for example from E. Mutschler, Arzneimittelwirkungen, Lehrbuch der Pharmakologie und Toxikologie, Stuttgart, (1991), page 660, bottom right-hand column, that when administering cyclosporin or cyclosporin A orally, the bioavailability is only about 35%. Cyclosporins are substances of strongly hydrophobic character. Because of their poor water solubility, there are extreme difficulties in processing these compounds with the usual pharmaceutical excipients into preparations having sufficient bioavailability.

[0007] Generally, cyclosporin-containing medicaments proposed so far are based on the use of an alcohol and/or oils or similar carrier substances in conjunction with one or several surface-active substances. In this way, perorally administrable preparations or also injection preparations are produced.

[0008] In e.g. the German Red List 1995 (Rote Liste 1995, Aulendorf), a drink solution is described, which has a content of cyclosporin and ethanol, wherein Labrafil M1944CS or M2125 based on polyoxyethylene-7-glycerol-trioleate or is present as surfactant. This solution additionally contains corn oil or olive oil. The solution is also used to fill gelatin capsules for peroral administration.

[0009] A disadvantage of known commercially available cyclosporin preparations for injection is that they are poorly tolerated by some patients owing to the frequent occurrence of anaphylactic reactions (Kahan et al., Lancet, 1984 I:52; Leunissen, K. M. et al., Lancet, 1985, 1:636).

[0010] WO-92/09299 relates to perorally administrable liquid medicaments which contain a cyclosporin with a mixture of a hydrophilic solvent and a surface-active substance in the form of polyoxyethylene-polyoxypropylene block polymers (poloxamers, with a molecular weight of 1000 to 15,500). A disadvantage of these formulations is the precipitation of the active ingredient upon contact with aqueous solutions.

[0011] A cyclosporin capsule preparation is also known which contains as carriers and excipients, apart from ethanol and propylene glycol, various corn oil glycerides, glycerin and macrogol-glycerol-hydroxy-stearate, as well as α-tocopherol.

[0012] From DE-OS 39 24 207, the contents of which are incorporated herein by reference, cyclosporin-containing preparations are known for intravenous administration, with one or several polyethylene glycol derivatives having the hydroxy-fatty acid moiety bonded in the molecule, together with one or several alcohols as cosolvent. The preferred surfactant in the form of the polyethylene glycol derivative is polyethylene glycol-660-12-hydroxy-stearate. However, a series of other polyethylene glycol derivatives are also disclosed, e.g. polyethylene glycol-9-hydroxy-myristate or polyethylene-glycol-9-hydroxy-palmitate.

[0013] The preparations having this composition represent injection concentrates, as disclosed in detail in particular in example 1. These concentrates indicated as drug preparations contain for example 4.85% by weight of cyclosporin A, which when used for intravenous application, has to be diluted prior to the injection with an isotonic solution of saline, glucose, dextran, fructose or mannitol. To the person skilled in the art, it is clear that these concentrates have to be diluted to an extent such that they correspond to the isotonic requirements of injection solutions that are to be administered intravenously (corresponding to the isotonic state of a physiological saline solution). There is no disclosure in this patent specification of a possibility of using these undiluted injection concentrates directly as medicaments or peroral administration.

[0014] The preparations described are concerned exclusively with intravenously administrable formulations. The disadvantage of these preparations is that they have to be administered in clinics by trained personnel.

[0015] The present applicants have found particularly interesting compositions useful for not only cyclosporins but also macrolides.

[0016] Preferred cyclosporins for use in the compositions of this invention are cyclosporin A and ([3'-desoxy-3'-oxo-MeBmt]$^{1}$-[Val]$^{2}$-Ciclosporin), the latter disclosed and claimed in EP 296 122.

[0017] Rapamycin is an immunosuppressive lactam macrolide produceable, for example by *Streptomyces hygroscopicus*. The structure of rapamycin is given in Kesseler, H., et al.; 1993; *Helv. Chim. Acta;* 76: 117. Rapamycin is an extremely potent immunosuppressant and has also been shown to have antitumor and antifungal activity. Its utility as a pharmaceutical, however, is restricted by its very low and